mg of conjugated estrogen of 10 μg of ethinyl estradiol a day for the first 21 days of each month. In view of the association between long-term unopposed estrogen therapy and endometrial pathology, including carcinoma, we recommend the addition of a progestin (medroxyprogesterone acetate, 5 mg a day) to the estrogen therapy from day 12 through day 21 of each month.[1,9-11]

Many questions about long-term estrogen-progesterone therapy remain to be answered in patients with Turner's syndrome. Prominent among these are, What is the minimal effective dosage of estrogen and progesterone? Which estrogens and progestins are safest for chronic replacement? To what age should replacement continue? Finally, long-term follow-up may shed increased light on the prevalence of and factors that predispose to other associated problems, such as hypertension not caused by coarctation of the aorta, osteopenia, inflammatory bowel disease, rheumatoid arthritis, Hashimoto's thyroiditis and diabetes mellitus.

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Flawed Theories in a Real World

AT THIS WRITING it appears that another theory, call it social, economic or political, is running up against realities poorly understood by the theorists. This time it is the theory of "supply side economics" that seems not to be working the way its advocates expected, and may or may not ever work at all. This is only one of a long line of social, economic and political theories that have been conceived (often in ivory towers), tried in the real world (often by government fiat) and found to fall far short of the expectations of the proponents. Could it be that there is some fundamental flaw running through many or even all of these theories?

From the perspective of this one physician the flaw might well be a failure to understand that the real world of human society is a social, economic and political system made up of people who in turn have individual natures and function individually and together in ways we call human. Their natures and their human functioning are fundamental and inescapable characteristics of the people who make up the system, and by extension they must be the essential characteristics of the human societal system itself. If this is true, it may explain why many of the social, economic and political theories that are developed and implemented do not work in the real world. The mystery of their failure may be solved when the real world is analyzed and better understood in terms of the human, even biological, society it has to be. Biological science addresses a biological system *as it is,* and shapes and tests its theories on the basis of what is known to be, rather than the opposite—that is, what *is assumed to be* on the basis of one or another conceptual theory. The real world is real indeed, and one cannot help wondering if much social, economic and political theory is not based on unreal, perhaps even unbiological, assumptions, and is thus flawed. If this is so, it may be little wonder that when such theories are tried out in the real world they fall short of the expectations of their proponents, and do not work well or at all.

—MSMW

Calcium Channel Blockers and Cardiovascular Therapeutics

IN 1962 not many pharmacologists and clinicians would have thought that the drug verapamil, introduced in that year as a powerful new smooth muscle relaxant and coronary vasodilator, might represent the prototype of a class of compounds that would make a far-reaching impact on the treatment of many cardiocirculatory disorders.[1] Little was known then about the role of the slow-inward calcium channel in cardiac muscle. Selective coronary angiography was in its infancy.

Provocative tests for evaluating vasospastic propensity in rest angina had not been conceived, though Prinzmetal[2] recently had postulated a role for coronary artery constriction as a basis for the so-called variant angina. Myocardial perfusion imaging had not been developed to document clearly that primary decreases in myocardial blood flow could indeed occur in certain types of angina. Moreover, it was not until the early 1970's that His bundle electrocardiography established the reentrant nature of paroxysmal supraventricular tachycardia.[3]

An important advance was made in 1970 by the voltage clamp technique when it was established that the inward depolarizing current in cardiac muscle was separable into two components.[4] The charge carrier for the fast current was established as sodium ions, the influx of which is blocked selectively by tetrodotoxin and local anesthetic agents. For the slow channel the charge carrier was found to be essentially calcium. It was soon discovered that the slow channel, responsible for excitation-contraction coupling in cardiac muscle and in part for the long plateau phase of the cardiac action potential, could be inhibited specifically and selectively by certain metals such as manganese and cobalt but, more important, by the drug verapamil and its methoxy derivative D_{600}.[4] An appreciation of this phenomenon has led to the delineation of a class of drugs ("calcium antagonists") that, while being chemically heterogeneous, share the common properties of blocking the myocardial slow channel and of inhibiting calcium influx in smooth muscle to varying degrees. Such effects are particularly prominent in isolated tissues, but the in vitro effects are modulated to the extent that the profound negative ionotropic actions of this class of agents is all but nullified (except in the case of severely depressed ventricular function) by the potent vasodilator effects acting to reduce ventricular afterload.

In patients calcium antagonists may produce a complex interplay of simultaneous changes in hemodynamic variables and electrophysiologic measurements. The net effects may vary with each compound, with the level of the autonomic tone (some of the agents, such as diltiazem and verapamil, are noncompetitive sympathetic antagonists), with the level of ventricular function and with the presence or absence of myocardial ischemia. Various calcium antagonists differ also with respect to their potentials for producing vasodilation or for blocking atrioventricular (AV) conduction. An appreciation of such pharmacologic differences and similarities provides the rational basis for the expanding role of calcium antagonists in cardiovascular treatment.

In this issue of the journal, Dr. Deedwania discusses the electrophysiologic and hemodynamic actions of calcium antagonists relative to their clinical applications. A glance at the list of main indications for use—cardiac arrhythmias, ischemic myocardial syndromes, hypertension, hypertrophic cardiomyopathies and possibly myocardial preservation—clearly suggests that the overall spectrum of the therapeutic use of calcium antagonists may well rival that of β-adrenoceptor blocking drugs. However, the therapeutic uses of these drugs and of β-antagonists are not mutually exclusive except in certain well-defined clinical situations. It is worth emphasizing that for most clinical indications the fundamental mechanisms underlying the observed salutary effects of calcium antagonists differ from those of β-antagonists. For example, unlike β-antagonists, calcium antagonists are potent coronary vasodilators and a clear rationale exists for their use in vasospastic angina. This is vindicated by clinical studies and experience on the role of these compounds in angina is likely to increase if the observations of Maseri and colleagues[5] are confirmed. They state that Prinzmetal's angina is only one spectrum of vasospastic ischemic myocardial syndromes. However, it is not known how much more effective these agents are compared with the longer acting, newer preparations of nitrates with better bioavailability. In the case of chronic stable angina, an increasing number of reports indicates that in maximally tolerated dosages, β-antagonists and calcium channel blockers have comparable efficacy. However, β-blockers act essentially by reducing myocardial oxygen consumption as indicated by decreases in the heart rate-blood pressure product at rest and with exercise. For a given effect on angina, calcium antagonists cause less reduction of this product, indicating that the overall antianginal effect is only in part related to a reduction in the gross indices of myocardial oxygen consumption. Other factors may mediate their salutary actions in ischemic syndromes.

As indicated by Dr. Deedwania, calcium antagonists, particularly verapamil, will become the drugs of choice in the rapid termination of paroxysmal supraventricular tachycardia.[6] The success rate for this indication may approach 80

percent to 100 percent when verapamil is given appropriately. The mechanism of the termination is an abrupt block of anterograde conduction in the AV node,[7] the weakest limb of the tachycardia circuit. Diltiazem is less effective in this regard and nifedipine not at all, reflecting the varying effects of these compounds on AV nodal conduction and refractoriness. For other clinical indications, however, nifedipine will be the preferred agent when conduction system disease such as the sick sinus syndrome is present.

Not emphasized by Dr. Deedwania is that, as a group, calcium antagonists have little electrophysiologic effect on the ventricular myocardium; thus they are rarely effective in ventricular arrhythmias except when such dysrhythmias arise on the basis of myocardial ischemia, especially in the wake of coronary vasospasm. In this setting, calcium antagonists may well become first-line drugs in contrast to their limited role in nonischemic ventricular tachyarrhythmias. Of interest is that while these agents, either alone or in combination with β-antagonists, are effective in controlling symptoms in patients with hypertrophic cardiomyopathy, they appear to have little effect on cardiac arrhythmias complicating this disorder. It is unknown whether there is a regression of hypertrophy during chronic therapy.

As indicated by Dr. Deedwania, the data are still scant on other disorders such as arterial hypertension, pulmonary hypertension and congestive cardiac failure, which constitute potential clinical indications for calcium antagonists. More definitive studies are needed to delineate their precise therapeutic roles in this regard. However, it is inherently unlikely that these compounds will, or indeed should, be used for the control of congestive cardiac failure in preference to the plethora of safer vasodilator drugs already available, unless further work shows unequivocal advantages in the case of calcium antagonists in this setting. It should also be indicated that in patients with congestive cardiac failure, digitalis glycosides are nearly always used and that the concomitant use of oral calcium antagonists and digoxin has recently been shown to elevate serum digoxin levels by reducing renal clearance of the glycoside.[8] Thus, the chronic use of calcium antagonists in congestive failure must always allow for such a drug interaction that may induce digitalis-toxic cardiac arrhythmias.

One of the appealing features of calcium antagonists is that as a class of compounds they do not aggravate bronchospasm or interfere with carbohydrate metabolism, nor do they worsen the symptoms of peripheral arterial insufficiency. Indeed, they may even exert a beneficial effect in Raynaud's phenomenon. In these respects, for patients who have such associated complications and yet need treatment with β-blocking drugs for arrhythmias, hypertension, idiopathic hypertrophic subaortic stenosis (IHSS) and ischemic myocardial syndromes, the introduction of orally administered calcium antagonists in the United States is undoubtedly a significant therapeutic advance because their overall spectrum of clinical effects is very similar to those of β-antagonists.

In the case of β-antagonists, there is increasing evidence that the incidence of sudden cardiac death can be reduced significantly by the chronic prophylactic treatment of the survivors of acute myocardial infarction.[9] There is little to suggest that such a beneficial effect is mediated through a direct influence on arrhythmias; the presumption is that the primary action is on ischemia with a secondary effect on electrical instability.

Calcium antagonists are potent antianginal drugs with the additional propensity for reversing coronary vasospasm; like β-blockers, they exert a protective effect on the ischemic myocardium. The question therefore has arisen whether they may also reduce the incidence of sudden cardiac death in the survivors of acute myocardial infarction and in other subsets of patients with ischemic heart disease. A decisive answer to this question is likely to be of far-reaching importance with regard to the expanding role of calcium antagonists in cardiovascular therapeutics.

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